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Prevalence of atopy in children with celiac disease

Ayse Senay Sasihuseyinoglu[1], Mehmet Agın[2], Zeliha Haytoglu[3], Aylin Ozhan[1], Gokhan Tumgor[2], Mahir Serbes[1], Dilek Dogruel[1], Derya Ufuk Altıntaş[1]
[1]Department of Pediatric Allergy and Immunology
[2]Department of Pediatric Gastroenterology, Hepatology and Nutrition
[3]Department of Pediatri, Faculty of Medicine, Cukurova University, Adana, Turkey

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Abstract
Aim: Celiac disease (CD) is an autoimmune disorder caused by dietary gluten. There are only a few studies reporting on the prevalence of atopy in CD and the results are conflicting. The aim of this study was to examine the prevalence of atopy in CD patients.
Material and Methods: A total of 97 children with confirmed CD and a control group of 95 age- and gender-matched healthy controls were included in the study. The immunoglobulin (Ig) A-G-E-M levels, complete blood count, Phadiatop and milk-egg-rice-wheat specific (sp) IgE were assessed and skin prick tests (SPTs) were applied.
Results: The CD patients comprised 51 (52.6%) girls and 46 (47.4%) boys with a mean age of 10.3 ± 4.8 (range, 1-16) years. The median level of IgE, total eosinophil count, Phadiatop, food sp IgE, and SPT positivity were significantly higher in CD patients compared to healthy controls (p=0.001, p=0.001, p=0.001, p=0.001, p=0.013, respectively). No positive reaction was detected in any of the participants in the oral food challenge test. The prevalence of atopy in the CD patients was higher than that of control group (29.9% vs. 11.0%). Moreover, six patients with CD were diagnosed with allergic diseases.
Discussion: The incidence of atopy was found to be higher in CD patients than in healthy children.

Keywords
Atopy; Celiac disease; Child; Wheat

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Corresponding Author: Ayse Senay Sasihuseyinoglu, Cukurova University, School of Medicine, Balcalı Hospital, Department of Pediatric Allergy and Immunology, 01330, Sarıcam, Adana, Turkey.
E-mail: ssashuseyinoglu@yahoo.com.tr P: +90 5066083040 F: +90 322 338 69 00
Corresponding Author ORCID ID: https://orcid.org/0000-0003-4085-0256

Introduction

Celiac disease (CD) affects 0.6% to 1% of the world population [1]. In a study which included 20190 students aged 6-17 years screened in various regions of Turkey, the prevalence of CD diagnosed by biopsy with antibody positivity was found to be 0.47% [2]. CD is caused by dietary gluten which is found in wheat in genetically predisposed individuals carrying the human leukocyte antigen (HLA) DQ2 or DQ8 [1]. Consumption of gluten proteins (gliadins and glutenins) induces a T-cell mediated inflammation of the small intestine in CD [3]. Although the relationship between CD and allergy remains unclear, some reports suggest that patients with CD have an increased frequency of allergic manifestations compared with the general population [4,5]. Moreover, CD and allergy might share a similar predisposing background [6]. The aim of this study was to evaluate the prevalence of atopy in CD.

Material and Methods

Study population

All children followed up with a diagnosis of Celiac disease in the pediatric gastroenterology clinic, and the healthy children who applied to the social pediatrics clinic for the group were referred to the pediatric allergy clinic during the study. CD was diagnosed based on the accepted guideline [7]. Atopy was defined as a personal tendency to produce immunoglobulin (Ig) E antibodies in response to exposure to common allergens, with an increased risk of developing typical diseases such as asthma, allergic rhinitis, atopic dermatitis, or food allergy (FA). The presence of serum allergen-specific (sp) IgE antibodies and/or positive skin prick test (SPT) was accepted as an indicator of atopy [8]. The diagnosis of asthma was made according to the Global Initiative for Asthma (GINA) guidelines. Asthma was diagnosed in the presence of asthma symptoms (respiratory distress, wheezing, wheezing or shortness of breath after exercise) within the last one year, in the detection of a 12% increase in forced expiratory volume in 1 second (FEV1) after bronchodilator inhalation, and in children with a history of regular medication for asthma within the last one year. Allergic rhinitis was defined as the presence of immunologically mediated hypersensitivity symptoms of the nose such as itching, sneezing, increased secretion, and blockage [9]. Throughout the study, no medication was used by any patient. All the participants completed a questionnaire that included items probing their demographic characteristics. The IgE, IgA, IgM, and IgG levels, complete blood count, phadiatop® and milk-egg-rice-wheat sp IgE were measured in all participants. SPT was performed using the same antigens for all participants. Food challenge tests were performed in children with suspected FA.

Laboratory analysis

The IgE, IgA, IgM, and IgG levels were measured using nephelometric immunoassay. Eosinophil count measurements were performed using a Coulter Hmx Haematology Analyzer (Beckman Coulter, Inc., CA, USA). Eosinophilia was diagnosed in the detection of >0.45x109 eosinophils/L and an eosinophil ratio of >4% in peripheral blood. Serum concentrations of IgE against cow's milk, hen's egg, wheat, rice allergens were analyzed using an ImmunoCAP ® kit (InVitroSight, Phadia AB, Uppsala, Sweden).

Serum concentrations of IgE against common inhaled allergens including fungi, pollens, insects and dust mites were analyzed using Phadiatop®. The detection of sp IgE antibodies exceeding 0.35 kUA/L indicated a positive result.

Skin prick test

Participants were considered eligible for SPT if they had not received antihistamines for at least one week. SPT was performed using a commercial extract and was applied epicutaneously for Dermatophagoides pteronyssinus, Dermatophagoides farinae, tree pollens (Alnus glutinosa, Betula verrucosa, Coryllus avellena, Populus alba, Quercus robur, Olea europa, Fagus silvatica), grass pollens (Lolium perenne, Cynodon dactylon, Phleum pratense, Poa pratensis, Festuca pratensis, Alopecurus pratensis, Secale sereale, Triticum sativum), moulds (alternaria, penicilliumi mucor, candida, aspergillus, cladosporium), milk, egg, rice, and wheat (Allergopharma, Rheinbek, Germany). Histamine was accepted as a positive control and saline was accepted as a negative control. SPT was considered as positive if the mean wheal diameter was ≥3 mm compared with the negative control after 20 min.

Food challenge test

Food allergy (FA) was suspected in children with a serum sp IgE ≥0.35 kUA/l and in children with a positive SPT by food [9]. The double-blind placebo-controlled food challenge (DBPCFC) test was performed in children with suspected FA and was not performed in CD patients with suspected wheat allergy. Both the active food and the placebo food were given on two separate days. Prior to testing, children were given an elimination diet free of the considered allergenic foods for 15 days. The suspected food was administered starting at a minimum amount, and then incremental doses were given at 20-min intervals until the total challenge dose was tolerated or an adverse reaction occurred. The starting dose of the food was determined according to the history of reaction intensity or the results of sp IgE or SPT. The total dose administered was the age-adjusted normal daily intake of the food. The infants were observed for at least 2 hours after the last dose before going home. Parents of all children were contacted by telephone 72 hours and one week after test completion in order to determine the findings suggestive of FA that could be defined as positive when urticaria, angioedema, vomiting, diarrhea, eczema or respiratory and cardiovascular symptoms developed during the challenge procedure.

Statistical Analysis

Data were analyzed using SPSS 15 for Windows (SPSS Inc. Chicago, IL, USA). Descriptive values were expressed as mean ± standard deviation (SD) and median (minimum-maximum) for continuous variables and as frequencies (n) and percentages (%) for categorical variables. Categorical variables were compared using the Chi-square test. The groups' serum IgE and food sp IgE concentrations were compared using the Mann-Whitney U test. A p-value of <0.05 was considered significant.

Ethical approval

This study was approved by the local Research Commission and Ethics Committee (Date: May 13, 2016; No: 6/53). The study protocol was conducted in accordance with the Declaration of Helsinki [10]. Informed parental consent was obtained from all the participants before inclusion.

Results

A total of 97 children with confirmed CD and a control group of 95 age-and gender-matched healthy controls were included in this study. The CD patients comprised 51 (52.6%) girls and 46 (47.4%) boys with a mean age of 10.3 ± 4.8 (range, 1-16) years. All patients with CD were in clinical remission and were on a gluten-free diet. Atopy was detected in 29.9% and 11% of the CD patients and control subjects, respectively, and this difference was statistically significant (p=0.02). In the CD group, six patients were diagnosed with an atopic disorder (both allergic asthma and allergic rhinitis in 2, allergic asthma in 2, and allergic rhinitis in 2 patients). Accordingly, the prevalence of atopic disorder was significantly higher in the CD group compared to the control group (p=0.029).

Table 1. Demographic, Clinical, and Laboratory Characteristics

	CD	Control group	p
Number of participants	97	95	
Age (years) (mean±SD)	10.2±4.8	9.2±2.3	0.6
Male/female	46/51	47/48	0.7
Immunoglobulins			
Ig A (mg/dl) (±SD)	116 ± 73.28	105.7 ± 63.26	0.59
Ig G (mg/dl) (±SD)	1031 ± 250	868 ± 277	0.55
Ig M (mg/dl) (±SD)	108 ± 51.7	117 ± 48.7	0.54
IgE (mg/dl) (±SD)	253±54	60±128	0.005
High IgE (n)*	31	5	0.001
Eosinophil count (median)	210 (20-1970)	150 (0-940)	0.001
Eosinophil rate (%) (median)	3% (0.2-19.3%)	1.7% (0-13.8%)	<0.001
Phadiatop (%)	20	4,2	0.001
Food sp IgE positivity (%)	16.5	2.1	0.001
Milk sp IgE positivity (n)	4	0	0.12
Egg sp IgE positivity (n)	8	1	0.035
Rice sp IgE positivity (n)	7	0	0.014
Wheat sp IgE positivity (n)	7	1	0.035
Skin prick test positivity rate (%)	16.5	5.3	0.013
D. pter, D.far. (%)	11.3	4.2	
Polen	2.06	0	
Alternaria	0	1.05	
Milk	0	0	
Egg	1.03	0	
Rice	0	0	
Wheat	0	0	
DBPCFC (n)	12	2	
Milk	3	1	
Egg	4	1	
Rice	5	0	
DBPCFC positivity (n)	0	0	
Allergic disease (n)	6	0	0.029
Asthma (n)	2	0	
AR (n)	2	0	
Allergic asthma +AR (n)	2	0	
Allergic sensitization (%)	29.9	11	0.02

CD: celiac disease, Ig: ımmunoglobulin, sp: specific, D. Pter: Dermatophagoidespteronyssinus, D. Farinea: Dermatophagoidesfarinae, DBPCFC: double-blind placebo-controlled food challenge, AR: allergic rhinitis, *The total immunoglobulin level above +2 standard deviation (SD) according to age was as accepted hıgh level and below -2 standard deviation (SD) according to age was accepted as low level.

Demographic Features

Table 1 demonstrates the demographic, clinical, and laboratory characteristics of both groups. The mean follow-up period for CD patients was 23.6±27.67 (range, 4-144) months. A family history of allergic disorders was detected in 11 (11.4%) patients with CD reported, while no family history of allergic disorders was reported in the control group.

Laboratory Results

The median level of IgE was significantly higher in children with CD than in control subjects (59 vs. 25.5 IU/l; p=0.001). However, the mean levels of Ig A-G-M were similar and within normal ranges in both groups. The percentage and total counts of eosinophils were significantly higher in children with CD compared to control subjects (p=0.001). The percentages of Phadiatop and food sp IgE positivity were higher in children with CD than in controls (p=0.001 for both). Thirteen patients with CD had multiple food sensitivity.

Skin prick test

The percentage of SPT positivity was higher in children with CD than in controls (p=0.013). House dust mites were the most common allergens in both groups (11.3% and 4.2%, respectively). There was no reaction to food in SPT except for one patient with CD who showed a positive reaction to eggs. The results of skin test are shown in Table 1.

Food provocation test

In total, 14 DBPCFC tests were performed in 10 patients with positive SPTs and/or positive food-sp IgE. DBPCFC with wheat was not perfumed in patients with CD since they were on a gluten-free diet. Moreover, DBPCFC was not performed in four patients since they did not consent to undertake the test. No patient tested positive for DBPCFC.

Discussion

The results indicated that the prevalence of atopy in our CD patients was higher than in the control group (29.9% vs. 11.0%). A recent study on 2297 adult CD patients showed a possible association between CD and IgE sensitization to some food and inhalant allergens [11]. Moreover, CD patients had a higher prevalence of atopic disease such as asthma, allergic rhinitis, and were more sensitized against aeroallergens and food allergens, while no patient had FA. To our knowledge, there are several studies reporting on allergic disorders in CD patients. Our result is higher than in some studies and in line with some studies [5,12-15]. Cooper et al. investigated the prevalence of asthma, allergic rhinitis, and atopic dermatitis in children with CD and detected atopic disease (asthma and eczema) in 7% of the patients [14]. In a similar study, Yavuzyilmaz et al. reported that the frequency of atopic dermatitis was higher in CD patients than in control subjects [13]. Hodgson et al. found atopic asthma and eczema in 6 (17%) out of 35 patients with CD as opposed to 3% of control subjects with peptic ulcer [14]. Another study suggested that the impaired intestinal mucosal permeability of untreated CD patients might result in an increased flow of dietary antigens through the intestinal mucosa, stimulating food-dependent hypersensitivity or reversing the impaired intestinal permeability, which has been observed in some allergic patients, could break the tolerance to gluten, promoting the CD among the genetically predisposed

subjects [15]. The prevalence of FA in children ranges between 3-7%, with the majority of allergies caused by cow's milk, hen egg, soya bean, wheat, peanut, tree nuts, fish, and shellfish [16]. Gastrointestinal manifestations of FA include emesis, nausea, diarrhea, abdominal pain, dysphagia, food impaction, protein-losing enteropathy, and failure to thrive [17]. Similarly, classic symptoms of CD include gastrointestinal problems such as chronic diarrhea, abdominal distention, abdominal pain, malabsorption, loss of appetite, vomiting, and failure to thrive [18]. Gluten is the main structural protein of wheat, composed of two main fractions depending on their solubility in aqueous alcohols: the monomeric soluble gliadins and the poorly soluble glutenins [19]. Gliadins are supposed to be the active fractions of gluten, while they actually contain the immunogenic peptides [20]. A recent study by Pillon et al. suggested that the risk of CD increases among patients with severe FA [18]. In our study, although food sp IgE positivity rate was higher in the CD patients than in the control subjects, no food allergy was detected by DBPCFC.Wheat allergy (WA) is a common gluten-related disorder, which was classified in 2012 [21]. The mechanism in WA may be mediated by sp IgE or cellular immunoreaction [22]. WA is often associated with other allergic manifestations, such as asthma (48-67%) or allergic rhinitis (34-62%) [23]. Symptoms last from a few minutes to two hours following wheat consumption. In young children, gastroenterological manifestations such as vomiting, diarrhea, or abdominal pain are more common [24]. SPTs and sIgE in vitro assays are the first-level diagnostic tests for WA [24]. Moreover, oral food challenge is the gold standard for diagnosis of WA [25]. In food allergies, the elimination of allergen food from the diet may cause tolerance over time. In our study, no reaction was detected in SPT with wheat, while seven patients with CD had positive wheat sp IgE, which could be attributed to the ongoing gluten-free diet of the patients. Nevertheless, DBPCFC with wheat could be not be performed in these patients due to their ongoing gluten-free diet, which is a part of CD treatment. Accordingly, the exact prevalence of WA in CD patients could not be determined. Our study was limited due to several reasons. First, our study population was relatively small. Second, patients with CD were in clinical remission, and all of them were on a gluten-free diet until the diagnosis of CD, and thus DBPCFC with wheat could not be performed in these patients. In conclusion, the prevalence of allergic sensitization was higher in CD patients than in healthy controls. In CD patients presenting with the signs of allergic disorders (eczema, rhinitis, asthma), concomitant allergy tests may be helpful at the time of diagnosis. Given that patients with confirmed CD are more sensitized against wheat proteins, we suggest that wheat allergy tests could be interesting in diagnosing CD and then repeated regularly over time to determine if the patient is at risk of allergic manifestations in case of an accidental exposure. Further studies are needed to evaluate the relationship between atopy and CD.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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